

**Application No. 10/583,567**  
**Amdt. dated March 4, 2009**  
**Response to the Office Action of November 4, 2008**

### **REMARKS/ARGUMENT**

This response is submitted under 37 C.F.R. § 1.111 to the Office Action of November 4, 2008.

Claims 1 to 52 are pending in the application with claims 1-12, 19-28, 34-36, 39-42, and 45-47 having been amended, and claims 13-18, 29-33, 37, 38, and 48-52 having been withdrawn from consideration.

#### **1. Rejection under 35 U.S.C. § 112, First Paragraph**

Claims 1-12, 19-28, 34-36, and 39-46 have been rejected under 35 U.S.C. § 112, first paragraph, because, according to the Examiner, the specification, while being enabling for some compounds of formula (I), does not reasonably provide enablement for all compounds of formula (I). The Examiner emphasizes that there are working examples only for the compound of formula (I) wherein n is 2 or 3, A is -C(O)- or -CH<sub>2</sub>-, B is a phenylene, C is -O-, D is a linear, saturated or unsaturated hydrocarbon-based chain containing 11 carbon atoms in length, E and G are NH C(O)CH<sub>3</sub>; R<sup>1</sup> is H or C(O)CH<sub>3</sub>; R<sup>1</sup> is H or C(OH)CH<sub>3</sub>; R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, and R<sup>9</sup> are all H; and R<sup>8</sup> is SO<sub>3</sub>Na or fucose.

Claims 1, 7, 19, and 24 have now been amended to define further the scope of the compound of formula I based on the examples. A relative broadening of the scope has nevertheless been conserved by keeping some substituents that are not explicitly disclosed in the examples, but for which those skilled in the art would recognize that compounds exhibiting these substituents could be made without undue experimentation and with a good assurance of success,

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either because they are classical chemical equivalents of the exemplified ones, and/or because these substituents are found in natural nod factors.

In particular, natural nod factors are compounds having a lipophilic fatty acid chain linked to the oligosaccharide skeleton. The inventors have found that synthetic compounds, which differ significantly from the natural ones because they have a ring in position B of the chain, have a beneficial effect comparable to, or even better than, natural compounds associated with other advantages (e.g., industrial preparation, stability, etc.). The inventors have shown that it is the case not only when A = -CH<sub>2</sub>-, but also when A = -O-, which is even more unobvious, as it leads to a chain that is less lipophilic. Sulfur is less electronegative than -O- and therefore more lipophilic, i.e., closer to the lipophilic feature of the natural compounds. Replacing the -O- in position A with -S- is an evident choice for one skilled in the art, without undue experimentation, and leading to a predictably active compound.

The inventors have shown that introducing a ring in position B of the chain has a beneficial effect comparable to or better than natural compounds associated with other advantages (e.g., industrial preparation, stability, etc.). This is exemplified with a phenylene in position B. A skilled artisan would have deduced, produced, and tested without undue experimentation and with a good assurance of success other related rings in position B. Claim 1 is now directed to compounds wherein B is an arylene or naphthylene in order to meet the election requirement.

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The inventors have shown that compounds with an oxygen atom in position C are effective compounds. To replace the oxygen atom by sulfur or CH<sub>2</sub> would be evident to the skilled artisan as it would lead to a more lipophilic chain, closer to the natural LCO compounds.

The working examples disclose compounds of formula (I) wherein D is a linear, saturated or unsaturated hydrocarbon-based chain containing 11 carbon atoms in length.

Nevertheless, it is known from the prior art that natural nodulation factors (NFs) can be N-acylated with chains of fatty acids of various lengths, without eliminating their nodulation activities. As examples, rhizobial strains produce natural NFs that are N-acylated with C<sub>14</sub> fatty acids (*Rhizobium galegae*), C<sub>16</sub> fatty acids (*Azorhizobium caulinodans*, *Bradyrhizobium* strains, etc.), C<sub>17</sub> fatty acids (*Mezorhizobium* sp. N33), C<sub>18</sub> fatty acids (*Azorhizobium caulinodans*, *Bradyrhizobium* strains, etc.), C<sub>20</sub> fatty acids (*Rhizobium* sp. GRH2, *Rhizobium galegae*), C<sub>22</sub> fatty acids (*Mezorhizobium loti*) (see D'Haeze W. et al., 12 GLYCOBIOLOGY, No. 6, 79R-105R, Table 1 (2002)). Additionally, N. Dermont-Caulet et al. (PLANT PHYSIOL., May 1999, Vol. 120, p. 83, right column, and p. 89, figure 9) have shown that nodulation activity can be found with derived compounds having an N-acyl chain composed of 8, 12, 16, and 18 atom carbons respectively, even if the activity is weaker with a C<sub>8</sub> chain. The N-acyl chain in these compounds takes the place of the chain named A-B-C-D in the compounds of the invention, wherein A-B-C has a length from three to six carbon atoms. Therefore, activity is expected with a group D comprising from 2 to 20 carbon atoms, preferably 3 to 17 carbon atoms, and more preferably with a group D comprising from 7 to 15 carbon atoms (for support, see page 23, line 35).

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The inventors have shown that compounds where E and G =  $\text{NHC(O)CH}_3$  are effective compounds. The skilled artisan would have, without undue experimentation or inventiveness, synthesized and tested compounds wherein the oligosaccharide skeleton comprises glucose monomer(s) (E or G = OH), as glucose monomer is closely related to GlcNAc monomer and no loss of activity is expected. In the same way, moving from NHAc to OAc is a classical chemical switch.

Natural nod factors compounds exhibit  $\text{R}^1 = \text{H}$  or  $\text{CH}_3$  (*see D'Haeze supra*). The inventors have shown that their synthetic compounds exhibiting  $\text{R}^1 = \text{H}$  or  $\text{C(O)H}$  or  $\text{C(O)CH}_3$  are effective compounds. The skilled artisan would have easily and without undue experimentation extrapolated from the results shown by the inventors and from the structure of natural nod factors that  $\text{R}^1$  may be H,  $\text{CH}_3$ ,  $\text{C}_{1-6}$ -alkyl,  $\text{C(O)H}$  OR  $\text{C(O)CH}_3$  with a good assurance of success.

The inventors have exemplified the invention with compounds wherein  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$ , and  $\text{R}^9$  are all H. The possibility of broadening these substituents without loss of activity is shown at least partially in the article by N. Dermont-Caulet et al., 120 PLANT PHYSIOL. 83-92 (May 1999), which disclosed that the root-derived structures induced by natural nod factors from *S. meliloti*- (O-acetylated at the  $\text{C}_6$  position) and induced by derivative compounds with or without the acetylation were indistinguishable (p. 85, right column). Natural O-acetylated nod factors and derivative compounds without the acetylation show also a comparable activity of

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nodulation (figure 2, page 86). Furthermore, natural nod factors may exhibit C(O)CH<sub>3</sub>, C(O)NH<sub>2</sub>, H, manosyl, arabinosyl, fucosyl, glycerol substituents (*see D'Haeze supra*).

The working examples disclose compounds of formula (I) wherein R<sup>8</sup> is SO<sub>3</sub>Na or fucose. Nevertheless, it is known to those skilled in the art that natural nod factors may have different substituents in the R<sup>8</sup> position, including fucosyl, methylfucosyl, acetylfucosyl, arabinosyl, sulfate ester, hydrogen, carbamoyl, acetyl, etc. (*see D'Haeze supra*). The skilled artisan therefore would have synthesized and tested, without undue experiment and with a good chance of success, these substituents and the chemically equivalent ones in position R<sup>8</sup>.

In view of the above, it is requested that the rejection of claims 1-12, 19-28, 34-36, and 39-46 under 35 U.S.C. § 112, first paragraph, be withdrawn.

**2. Rejection under 35 U.S.C. § 102(a)**

Claims 1-12, 19-28, 34-36, and 39-47 have been rejected under 35 U.S.C. § 102(a) as being anticipated by Grenouillat et al., "Simple Synthesis of nodulation-factor analogues exhibiting high affinity towards a specific binding protein," 43 ANGEWANDTE CHEMIE INTERNATIONAL EDITION, No. 35, 4644-46 (Sept. 2004).

The present application is a national stage entry of PCT/EP04/14909 filed on December 22, 2004 and claims priority to French application 0315543 filed on December 30, 2003. The subject matter of claims 1-12, 19-28, 34-36, and 39-47 was disclosed in French application 0315543. The Examiner has pointed out that a certified copy of the foreign priority document has been received in French, but no English translation has been received.

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An English translation of French application 0315543 is enclosed herewith. It is the Applicants' understanding that the filing of this translation will be sufficient to remove the French article as a reference against the present application.

Accordingly, it is requested that the rejection of claims 1-12, 19-28, 34-36, and 39-47 under 35 U.S.C. § 102(a) as being anticipated by Grenouillat et al. be withdrawn.

In view of the foregoing, it is submitted that this application is now in condition for allowance, and an early office action to that end is earnestly solicited.

Respectfully submitted,



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